VIVEKANANDA GLOBAL UNIVERSITY, JAIPUR

1. **Name of Scholar:Pradeep Singh Negi**

2. **Registration number: VGU/2016/RES/SCH/Phy/805**

3. **Title of the Research Investigation: Image analysis in PET/MRI using T1 relaxation time and PET SUV parameters to improve cancer diagnosis**

4. **Faculty/Department/Subject:**

Supervisor
Dr. ShashiBhushan Mehta
Adjunct Professor, VGU, Jaipur
Email: sbm20@yahoo.com
Mob: +91- 9717474030
Consultant Bio-Technology
(PET Suite-Indraprastha Apollo Hospital),

Co-Supervisor
Dr. Amarnath Jena
Email: drjena2002@yahoo.com
Mob: +91- 9811072952
Sr. Consultant
(PET Suite-Indraprastha Apollo Hospital),

5. Objective and Scope of the Research Investigation (Approx. 500 words):

Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)

MRI is a powerful non-invasive imaging technique. It plays an important role in clinical practices for both diagnosis and monitor treatment response(Peters NH*et al.*,2008;Marinovich ML*et al.*,2012; Wu LM*et al.*,2012). The principle of MRI relies on the magnetic behavior of hydrogen nuclei.When the sample is placed within a strong static magnetic field and applied RF field at Larmor frequency, it will exchange energy with the sample, and a RF coil detects the signal, which is turn used to form radiological image. Whereas DCE-MRI is an imaging method where T1-weighted MRI scans are acquired dynamically after injection of an MRI contrast agent. DCE-MRI has been explored to distinguish between benign and malignant lesions at high temporal resolution (Riham H*et al.*, 2011);the basic principle being malignant tissue differs from benign tissue in its time response to contrast agents.Permeability factor or transfer constant across the vessel walls (K^{trans}) has been used in characterizing breast lesions and also monitoring treatment response (Iagaru A*et al.*, 2007;Veltman J*et al.*,2008; Intven M*et al.*,2015;Tudorica A*et al.*,2016). Accuracy of native$T1_0$ relaxation time of the breast tissue remains a corner stone in the measurement of pharmacokinetic parameters like K^{trans},a topic of great research interest.

Positron emission tomography (PET)/ Total lesion glycolysis (TLG)

PET on the other side is also a non-invasive imaging technique, which is also used in clinical practices for both diagnosis and monitor treatment response.PET measures the two annihilation photons that are produced back-to-back after positron emission from a radionuclide tagged tracer molecule, which is chosen to mark a specific function in the body on a biochemistry level. When analyzing the diagnostic capability of FDG PET (Fluoro Deoxy Glucose Positron Emission Tomography), the most common parameter which is end point analyzed is the maximum and mean SUV(Standardized Uptake Value) of the tumor(Bing *et al.*2013). TLG (Total Lesion Glycolysis) a product of SUV mean and MTV (Metabolic Tumor Volume) has been found to be a useful parameter reflecting total metabolic activity in each lesion(Helen H. *et al.*, 2012). As a result now researchers are focusing on TLG for assessing the metabolic activity in breast cancer for diagnosis and to assess treatment response.

PET/MRI

PET/MRI is the recent imaging innovation integrating two different imaging modalities PET and MRI. PET scanners use photomultiplier tubes (PMTs) to spatially localize gamma-ray absorption in a scintillation crystal. Unfortunately, for PET/MRI, PMTs are sensitive to magnetic fields and remained a challenge for integration till recently when clinical PET/MRI makes use of avalanche photodiodes (APDs) (R. Grazioso*et al.*, 2006).All the hardware components and assembly are optimized for seamless functioning of both PET and MRI detection. Hybrid Simultaneous PET/MRI (with 3T MRI) is a high potential system for comprehensive breast cancer evaluation(Jena A *et al.*, 2017; Taneja S *et al.*, 2014).The modality enables measuring tissue metabolism(with PET) in a single session along with routine as well as high temporal resolution DCE MRI for assessment of breast cancer

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patients.This helps to reduce "image registration problems", "scan time" and patient discomforts while providing a vast window to assess tumor biology (tumor microstructure& metabolism).

The proposed research work under this thesis is limited to improving "techniques of measurement of "K^{trans} in DEC-MRI" and "TLG measurement in FDG PET"by using integrated PET/MRI system. Native $T1_0$relaxation time plays an important role in measurement of K^{trans}. The work envisages to improve Native $T1_0$ relaxation timein the volume of interest through normalization of $T1_0$using multiple spatially placed phantoms. MTV that works on the basis of SUV threshold is a gross approximation of the metabolic tumor volume (MTV) that is used in the calculation of Total Lesion glycolysis (TLG).The present work envisages to improve the measurement of MTV by applying Fuzzy Based Rule System (FRBS) on the data set collected from PET and inputs based on tumor volume derived from MRI. This is expected to improve calculation of TLG. Thesestepswill help in improving diagnosis and response evaluation in cancer cases.

Objectives and Scope of the research Investigations:

1. Corrected T1 maps using multi-phantom arrangement in DCE-MRI
2. Creating FRBS system for measurement of modified TLG in PET system
3. Patient data analysis with corrected T1 maps and modified TLG in diagnosis and response evaluation
4. Evaluation of patient data to study impact on final results with and without "Corrected T1 maps", "modified TLG"

6. Proposed Methodology (Approx. 200 words):

Instrumentation

Simultaneous PET/MRI will be performed on the BiographmMR (Siemens, Erlangen, Germany). This system consists of a fully functional PET system equipped with avalanche photodiode technology and a 3T MRI scanner (Delso G *et al.*,2011). The MR scanner allows whole body coverage with multiple integrated radiofrequency surface coils and also features a high-performance gradient system (45mT/m) equipped with the Total Imaging Matrix coil technology (Pichler BJ *et al.*, 2006). The PET scanner has a spatial resolution of 4.3 mm at 1 cm and 5.0 mm at 10 cm (from transverse FOV) and a sensitivity of 1.47% at FOV center and 1.38% at 10 cm.

Patient population

Imaging data of forty women with histologically proved enhancing breast lesions on biopsy/FNAB who will be undergoing Simultaneous PET/MRI will form the material of this study.

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Proposed Methodology:

A. Native $T1_0$ normalization with multiple phantoms in DCE-MRI:

1. Design and create "multiple tube phantom" within the breast coil volume
2. Calculate normalization native $T1_0$ value of each voxel within the volume of Interest using "multiple tube phantom"
3. Use normalization native $T1_0$ value from step 2 to calculate modified pharmacokinetic parameters like K^{trans} using an in house developed software *(project no: IDP/MED/01/2009/ Dated 22nd January 2010).*
4. Analyze data with and without modified pharmacokinetic parameters

B. Modified TLG volume in PET system:

Modified TLG value will be created based on FRBS applying on "Tumors contours from PET" and, "T1 weighted Tumor EnhancedImage Data"obtained from Gd(Gadolinium) Contrast enhanced MRI and "Modified pharmacokineticK^{trans} volume" of the tumor.

1. MTV to be calculated by applying a set threshold.
2. Identify thresholds features from "Contrast Enhanced MRI" and "K^{trans} from DCE-MRI"
3. Create Handcrafted fuzzy rule based system(Mehta et al..2005,2008) to improve contour of MTV
4. Use FRBS based MTV to get modified TLG
5. Combined and analyze patient data for diagnostic accuracy and reliabilityusing modified "K^{trans}" and "TLG"

Importance of Proposed Research Investigation/ Expected outcome (Approx. 200 words):

Expected output and outcome of the proposal

PET/MRI imaging suite, compliments the strength of each modality, gives more confidence in diagnosis and response therapy. This upcoming system helps to avoid repositioning error, saves time to increase machine throughput and increase patient comfort. In routine, Pharmacokinetic parameters (K^{trans}, v_e, K_{ep}) and PET parameters (SUV, TLG) are in use for patient study. But there are challenges and errors in calculating Pharmacokinetic parameters and TLG measurementsand it is the same for PET/MRI system. The proposed research will help to improve K^{trans} and TLG values from PET/MRI system. These improved pharmacokinetic and TLG parameters will enhance the diagnostic value and response evaluation for cancer cases.

The outcome of research will be:

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1. Creation of multiple phantoms which will be used to obtain corrected native $T1_0$ normalization value of volume of coil
2. Modified K^{trans} value of the tumor volume in DCE-MRI
3. Rule based system to improve TLG estimation
4. Patient data analysis using step 2 and 3 in diagnosis and response evaluation.

7. Review of the work related to the field of Research- already done on the subject -Present and Past Status (Approx.200 words):

Review of studies onNative $T1_0$

One major challenge in the use of quantitative DCE MR imaging is the non-uniformity of the radiofrequency transmit field (B1 +) observed across the breasts (Bedair*et al.*, 2016). This causes right-to-left variation in the flip angle,which results in regional signal intensity increase and/or decrease. The B1 inhomogeneity in VFA (variable flip angle) measurement can lead to substantial (around 52%) deviation in the T1 value of fat. In the event of tumors, a 1% increase in T1 could result in a 1% decrease in K^{trans} because the measured K^{trans} value is very sensitive to the T1 value as reported by Tofts PS *et al.*,1995. It was thought that B1 inhomogeneity is of little importance at 1.5 T (Sung K*et al.*,2013). Therefore, no routine recommendation of B1 correction T1 has been recommended.B1 correction for more accurate T1 values should be considered for quantitative dynamic contrast-enhanced breast MR imaging, even at 1.5 T, to offset significant systemic error(Wan-Chen Tsai *et al.*,2016). One major challenge in the use of quantitative DCE MR imaging at 3T is the nonuniformity of the radiofrequency transmit field (B1 +) observed across the breasts(Rahbar H*et al.*,2013). Kuhl et al. reported a right-left signal intensity difference in breast lesions by a factor of two at 3 T due to B1 inhomogeneity (Kuhl CK*et al.*,2007). This effect has been reported at 1.5 T, although to a lesser extent (El Khouli RH*et al.*, 2009). Numerous approaches have been proposed to mitigate the B1 non-uniformity effect. These include specially designed volume coils and the use of B1 +-insensitive adiabatic pulses (Hancu I *et al.*, 2010 and StaewenRS,*et al.*,1999). B1 correction demonstrates a substantial effect on the results of quantitative dynamic contrast-enhanced analysis of breast tissue at 3 T, which propagates into the pharmacokinetic analysis of tumors(ReemBedair*et al.* ,2016).

Computing native relaxation time $T1_0$

Native relaxation time T_{10} of the tissue (before contrast) is calculated using two flip angle at fixed $T_R$as per the equation 1, 2 (Deichmann R Haase A*et al.*,1992; Rakow-Penner R *et al.*, 2006)

$$T_{10}^{-1} = \frac{1}{TR} \ln \left[\frac{S_R Sin\alpha 2 Cos\alpha 1 - Sin\alpha 1 Cos\alpha 2}{S_R Sin\alpha 2 - Sin\alpha 1} \right] \qquad (1)$$

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$$S_R = \frac{S_{\alpha 1}}{S_{\alpha 2}} \quad (2)$$

$S_{\alpha 1}$ is the intensity value at α1 (2 degree flip angle) and $S_{\alpha 2}$ is the intensity value at α2 (15 degree flip angle) in the image sequence VIBE in the image acquisition protocol used for the calculation of T_{10}.

Normalizing Native T1 relaxation

The following methodology was used by Jena *et al.*, 2017 for the calculation of pharmacokinetic parameters using an externally placed single phantom. An externally placed phantom bottle filled with contrast with known nativeT_1 relaxation time at 3T (Provided by the manufacturer) was placed along with the coil and imaged during the examination for purpose of correcting the intrinsic tissue T_1 value later during evaluation.

A normalization technique was incorporated in the scheme for the optimization of native T1 relaxation time of the breast tissue. The detailed calculations are as follows:

Here, we used prefilled phantom with known contrast content and T_1 relaxation time (280 msec). Also the T_1 relaxation time of prefilled phantom is computed with the help of MRI system and equation 1, 2 called modified value (T_{1M}). Difference between the modified value T_{1M} and the known/predefined T_1 value gives a deviation factor that is caused by variation in machine parameters such as coil, magnet, and sequence, among other parameters. When a patient is placed in the MRI system, intrinsic value T_{10} of the tissue under consideration is computed without administration of the contrast agent. As is the case with the T_1 value of the phantom, the computed intrinsic T_{10} value of the tissue could also be influenced by the machine parameters and therefore a correct intrinsic T_{10C} value is computed by normalizing the computed intrinsic T_{10} value by the deviation factor calculated using the phantom. As an example, if the predefined T_1 value of the phantom is 30 and the modified value T_{1M} is 35, the deviation factor would be 5/30, which is 0.1666. In such a case, if the intrinsic T_{10} value is 100, the correct intrinsic T_{10C} value would be 83.33. The corrected intrinsic T_{10} can be used to calculate more precise value of $C_{gdtissue}$ at each temporal time point which can in turn be used for the calculation of pharmacokinetic parameters like K^{trans}, k_{ep} and v_e.

18-FDG PET in breast cancer imaging

^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been widely utilized for the diagnosis, whole body staging and restaging of different types of cancer(Almuhaideb A *et al.*, 2011;Agarwal A *et al.*, 2015;Mohan K *et al.*, 2011). Differently from conventional imaging methods capable of detecting only anatomical changes, ^{18}F-FDG PET is capable of providing information related to glucose metabolism in the various organs and tissues which effectively assist in the detection of distant metastasis(Zhu A *et al.*, 2011). Combining whole body PET and DCE MRI of breast with dedicated breast coil performed at different time points has been explored in breast cancer evaluation and found to be beneficial(Moy L*et al.*, 2010).

Hybrid Simultaneous PET/MRI (with 3T MRI in the core), it is now feasible to acquire anatomical, functional, and metabolic data in same spatial and temporal domain which is proving to be a high potential area for comprehensive breast cancer evaluation(Vogel WV *et al.*,2016). Also availability of metabolic and functional parameters at the

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same time frame holds promise in understanding interrelationship of imaging biomoarkers that could impact treatment planning and non invasive research.

SUV is the most common measure of metabolism through volume based measurements. However, this needs improvement as threshold levels may not be accurately calculated. Studies have alsoshown the usefulness of TLG and MTV for evaluating treatment response and diagnosis in different tumors (Roedl JB *et al.*, 2008; Erdi YE *et al.*,2000; Veit-Haibach P *et al.*, 2010; Guillem JG *et al.*,2004; Melton GB *et al.*,2007; Benz MR *et al.*,2008; Flamen P *et al.*,2008).

Calculation SUV, MTV and TLG

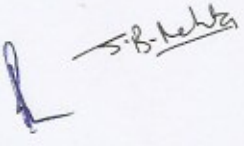
Evaluation of PET images

For evaluation of PET parameters generally(Tancja *et al.*, 2014) a region of interest was drawn manually around the areas of abnormal hyper metabolism identified on PET images and the maximum, mean standardized uptake value (SUV max and SUV mean) and MTV (metabolic tumor volume in$cm^3$by contouring PET uptake of the primary tumor by adopting a fixed 40% threshold fraction of SUVmax. TLG (Total Lesion Glycolysis) was calculated as the product of MTVandSUVmean.

However, people have also adopted using a methodology tosemiautomatically delineate the tumor contours by using a threshold of 50% of the maximal SUV within the lesion. The results were checked by comparison with the fused CT images to determine if adjustment was needed in the percentage threshold. The volume, mean SUV, and maximum SUV of each lesion were assessed and recorded by the nuclear medicine physicians. (Helen H,*et al.*, 2012)

7. Research Gaps identified in the proposed field of investigation - Based on review (Approx. 100 words):

- Most of the studies targeting B1 inhomogeneity are mechanical studies and are mathematical relationships.We will utilize this as a platform for developing physical phantom in the biological realm of the patient and utilize it for the purpose of T1 normalization. This will in turn aid in the accurate calculation of pharmacokinetic parameters.
- Instead of using a single phantom for magnetic field correction which is generally used in the existing literature, we will employ multiple on each side of the breasts to normalize the T1 values. This will in turn work to nullify the effect of nonuniformity of the radiofrequency transmit field (B1). This will further aid in correct calculation of varied flip angle and T1 values finally which can be utilized for acquiring improved pharmacokinetic parameters.
- ^{18}F-FDG PET component (SUV) is a volume based analysis and may not depict the metabolic activity of the lesion due to incorrect threshold selection. TLG and MTV are emerging as better makers of tumor metabolic activity for which thresholds need to be correctly optimized. Therefore of ^{18}F-FDG PET component of PET/MRI will be modified using MRI and ktrans enhancing image for improved values of metabolic activity parameters like TLG and MTV.



8. **Chapter wise details of Proposed Research Investigation Ph.D. Thesis:**

Chapter 1

Introduction

Chapter 2

Review of Literature

Chapter 3

Rationale of the study

Aims & Objectives

Chapter 4

Modified T1 Map with multi phantoms

Chapter 5

Modified TLG value using hand crafted fuzzy rule based system

Chapter 6

Analyzing patients data with modified K^{trans} and TLG value

Chapter 7

Future research trend

Chapter 8

Summary and Conclusion

Chapter 9

References

Chapter 10

Publications

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9. **Expected duration of the investigation (Year wise schedule to be give):**

1. Literature review and identification of problem (6 months)
2. Multiple Phantom creations and creating normalized T1 map of the coil (6 months).
3. Calculation of modified TLG value using fuzzy rule based system (6 months).
4. Analyzing patient data using step 2 and 3(9 months).
5. Manuscript preparation and thesis writing (9 months).

10. **Facilities available for the investigation at scholar end and facilities required on campus:**

1. At Scholar end:

Imaging facility (Simultaneous PET/MRI system), patient data acquisition, Technical assistance

2. On Campus:

Statistical analysis

11. **Bibliography- At least 50 relevant references (Update):**

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Supervisor
Dr. ShashiBhushan Mehta
Adjunct Professor, VGU, Jaipur
Email: sbm20@yahoo.com
Mob: +91- 9717474030
Consultant Bio-Technology
(PET Suite-Indraprastha Apollo Hospital),

Co-Supervisor
Dr. Amarnath Jena
Email: drjena2002@yahoo.com
Mob: +91- 9811072952
Sr. Consultant
(PET Suite-Indraprastha Apollo Hospital),

Pradeep Singh Negi
NAME AND SIGNATURE OF SCHOLAR
DATE: 11/01/2017